# Turning point towards the sustainable production of HMF in water: metal salts for its synthesis from fructose and inulin

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**Abstract**

5-hydroxymethyl-2-furaldehyde is one of the top 12 bio-based chemicals, precursor of renewable monomers and biofuels. This key molecule can be obtained from the dehydration of monosaccharides and polysaccharides. In this work, the synthesis of HMF from fructose and inulin was investigated in the presence of a wide range of metal salts adopting a truly sustainable catalytic approach: water as reaction medium, appreciable substrate concentration (10 wt%), very low amounts of catalyst (1-3 mM) and microwave heating. Copper salts, in particular copper (II) nitrate, afforded the best performances in terms of both HMF yield and selectivity. The influence of the most important parameters (temperature, time and $Cu(NO_3)_2$ concentration) on the reaction performance was also investigated through a statistical modelling, which showed that the remarkable HMF yield of 54 mol% was reached at 188 °C after 9 minutes. Under these optimized reaction conditions, an analogous outstanding HMF yield was also achieved starting from the polysaccharide inulin.

**Keywords (5-8)**

5-hydroxymethyl-2-furaldehyde; metal salts; fructose; inulin; microwaves; response surface methodology.

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## Introduction

Up to now, fossil resources have represented the primary feedstock for industrial chemistry. However, considering their progressive depletion, environmental pollution and greenhouse effect, in recent years, the necessity to adopt renewable resources has become increasingly urgent. Biomasses represent an important alternative feedstock, being abundant, inexpensive and widespread, thus, always more efforts have been addressed to their conversion into valuable products, under the perspective of "bio-refinery".[1-4] In particular, 5-hydroxymethyl-2-furaldehyde (HMF) is one of the most promising renewable products. It has a very reactive structure due to the presence of the aldehydic and the hydroxyl groups and the furan ring, making it a key platform molecule for the synthesis of chemicals, biofuels, solvents and monomers.[5-8]HMF is obtained by the acid-catalyzed dehydration of C6 fraction of biomass, including monosaccharides, such as glucose and fructose,[9] and more complex polysaccharides, such as cellulose, starch and inulin.[10-14]The monosaccharides are the ideal substrates for the HMF synthesis. In particular, fructose is the best HMF precursor because it can be directly converted into this furan compound through the loss of three water molecules.[9] However, under acidic conditions, HMF can rehydrate, leading to levulinic acid (LA) and formic acid (FA), two of the most important by-products of this reaction. Moreover, it easily condenses with itself or with the sugar substrate and/or the reaction intermediates, leading to the formation of insoluble solids, called humins.[15] These side-reactions are significant in the aqueous medium,[16] thus, up to now, appreciable HMF yields have been obtained only carrying out the reaction at low substrate loading, in the presence of organic media,[17,18] biphasic systems[19,20] or ionic liquids.[21,22] However, these solvents show both economic and environmental problems, being in most cases high-boiling, expensive and toxic, whereas water remains the best appealing and sustainable medium. Industrial production of HMF is already available and carried out by AVA

Biochem, with a monophasic water-based hydrothermal process, which has been optimized and acknowledged as sustainable, efficient and robust and certainly economically advantageous.[23] Some challenging opportunities for the optimization of this water-based process remain still open, including: i) catalysis selection, e.g. finding new sustainable and efficient water-tolerant catalysts, and ii) HMF purification ones, the latter being mainly focused on technological improvements of the extraction unit operation, which should require also more sustainable bio-based solvents and new HMF purification strategies, preferably occurring directly in water phase. In this respect, an interesting patent reports the direct HMF purification from its aqueous solutions by adsorption on amine-based resins, with the aim of a linear polyethyleneimine polycation.[24] The next HMF desorption can be smartly carried out by a simple pH variation and without the use of an organic solvent, as previously investigated.[25] Regarding the catalysis issue, the C6 sugars dehydration to HMF has been performed in the presence of both homogeneous[19,21,26,27] and heterogeneous catalysts.[13,14,28,29] In the field of the homogeneous ones, in recent years, inorganic salts have shown to be active catalysts for the HMF synthesis in aqueous medium.[12,23,30-35] In fact, metal salts are readily hydrolyzed in water, according to equation 1,

$$[M(H_2O)_x]^{n+} + H_2O \rightleftharpoons [M(H_2O)_{x-1}(OH)]^{(n-1)+} + H_3O^+ \qquad \text{(eq.1)}$$

Thus, they can act as both Lewis and Brønsted acid catalysts, respectively, due to the presence of the unsaturated metal center, and to the protons released from the salt hydrolysis.[12,31,33] Some of the most important results reported on the dehydration of fructose and glucose in water in the presence of inorganic salts are summarized in Table 1.

Table 1, near here

The highest HMF yields have been ascertained starting from fructose rather than from glucose, and some investigations have been performed adopting microwave heating,[30,35]

which allows a significant reduction of reaction time and energy consumption.[12,30,35-37] Also the dehydration of the polysaccharide inulin has been studied under microwave irradiation. De et al. proved the effectiveness of $AlCl_3$ (139 mM) for the hydrolysis of inulin (5 wt%) in water, reaching, at 120 °C after 5 min, the HMF yield of 29 mol%.[30] On the other hand, Fachri et al. carried out the inulin conversion to HMF, in water and in the presence of 5 mM $CuCl_2$, approaching the highest HMF yield of 39 mol%, working at 180 °C for 10 minutes with a starting inulin concentration of 5 wt%.[12]

In this context, now the fructose dehydration to HMF in water has been studied under microwave heating, in the presence of different inorganic metal salts, in order to investigate the role of both anions and cations. The fructose concentration of 10 wt% was adopted, a value higher than the most ones reported in the literature, in order to increase HMF concentration in the reaction mixture, thus making the process more interesting for next industrial applications. In this perspective, also a very low amount of catalyst, in the range 1-3 mM, was adopted, and the optimization of the reaction parameters in the presence of the best catalyst $Cu(NO_3)_2$ was also studied through a statistical modelling approach. An analogous investigation was also performed starting from inulin, the first step to moving towards the direct exploitation of raw fructan-rich biomasses.

## Experimental Section

### Materials

5-hydroxymethyl-2-furaldeyde (95%) was supplied by AVA Biochem. Formic acid (99.8%), levulinic acid (98%), copper (II) sulfate (≥99%), potassium sulfate (≥99%), copper (II) chloride (≥99%), sodium chloride (≥99%), aluminum nitrate (≥98%), aluminum chloride (≥99%), nickel (II) sulfate (≥99%), nickel (II) chloride (≥98%) were purchased from Sigma-Aldrich. Potassium nitrate (≥99%), potassium chloride (≥99%), aluminum sulfate (≥98%), sodium nitrate (≥99%), nickel (II) nitrate (≥98%) and copper

(II) nitrate (≥99%) were obtained from Carlo Erba. Fructose was food grade. Inulin from *Dahlia Tubers* ($[\alpha]_D^{20}$ = -37.0 and $M_n$ ≈ 5,000) was purchased from Fluka. All chemicals were employed without any further purification.

**Dehydration reaction**

The dehydration reactions were carried out in a monomodal microwave reactor CEM Discover S-class System designed to contain a closed vessel that not provides for the possibility of sampling the gases evolved during the reaction. In a standard synthesis, an aqueous fructose or inulin solution (5 ml, 10 wt% substrate) was charged in the reactor vessel (10 ml) with the selected amount of salt. The vessel was heated at the stated temperature for the established time under magnetic stirring. At the end of the reaction, the vessel was rapidly cooled at room temperature, opened to the atmosphere and the reaction mixture filtered with a Buckner funnel, when the solid precipitate was present. Finally, the liquid phase was filtered through a syringe filter (Whatman 0.45 µm PTFE) and analyzed. The optimized reaction was also scaled up to the isolated HMF yield of about 1.5 g. Experimental details are reported in the Supporting Information.

**Analytical instrumentation**

High-pressure liquid chromatography (HPLC) analysis of the liquid samples deriving from dehydration reactions was carried out with Perkin Elmer Flexar Isocratic Platform equipped with a column Benson 2000-0 BP-OA (300mm x 7.8 mm). A 0.005 M $H_2SO_4$ aqueous solution was adopted as mobile phase, maintaining the column at 60 °C with a flow rate of 0.6 ml/min. The concentrations of products were determined from calibration curves obtained with standard solutions. Fructose conversion, products yield and products selectivity were expressed in mol% and, in the whole manuscript, the reported HMF yields were the HPLC-determined ones. The unidentified products included humins, soluble and insoluble compounds and gases, the last one not sampled due to the employed reactor which not provides the possibility of collecting the evolved

gases. Their yield (mol%) was determined through the following equation: [(converted fructose mol - HMF mol - FA mol)/starting fructose mol] × 100, being formic acid produced stoichiometrically in equimolecular ratio with levulinic one.

**Extraction and purity grade of HMF**

The isolated yield of HMF obtained in the optimized reaction (188 °C, 9 min, concentration of $Cu(NO_3)_2$: 3 mM) was evaluated by continuous liquid/liquid extraction of the aqueous mixture with dichloromethane as the extraction solvent. In a typical procedure, 20 ml of the hydrolyzate was treated with 60 ml of dichloromethane in a continuous liquid/liquid extractor apparatus for 4 h and then, once the organic fraction was separated, dichloromethane was removed by distillation under reduced pressure. Finally, the isolated yellow solid was recovered and weighted. A small amount of this extract was dissolved in deuterated chloroform and analyzed by $^{1}H$ NMR and $^{13}C$ NMR (Figure S1). The HMF purity grade of 94% was ascertained. On the basis of the weighted amount and taking into account the purity grade of HMF, the isolated HMF yield of 41.5 mol% for the optimized reaction was obtained, while the HPLC-determined yield was 54.0 mol%. Detailed $^{1}H$ NMR data (200 MHz, $CDCl_3$): δ = 2.99 ppm (s, 1H, −OH), 4.73 ppm (s, 2H, $-CH_2OH$), 6.53 ppm (d, 1H, −CH=), 7.21 ppm (d, 1H, −CH=), 9.59 ppm (s, 1H, −CHO). Detailed $^{13}C$ NMR data (200 MHz, $CDCl_3$): δ = 56.14 ppm (1C, $-CH_2OH$), 109.43 ppm (2C, =C−C=), 151.32 ppm (1C of double bond, =C−CHO), 162.10 (1C of double bond, $=C-CH_2-$), 176.91 (1C, −CHO).

**Statistical modelling**

The HMF synthesis from fructose employing $Cu(NO_3)_2$ as the catalyst was optimized through the response surface methodology (RSM). The set of experiments corresponded to an incomplete, factorial, centred experimental design. The selected independent variables and their respective variation ranges were established as follows: temperature

(T): 150-200 °C, reaction time (t): 5-25 min, concentration of $Cu(NO_3)_2$ (C): 1-3 mM. The initial fructose concentration of 10 wt% was a constant of the model. The respective dimensionless and normalized variables, including between (-1; 1), for temperature (denoted as $x_1$), reaction time (denoted as $x_2$) and salt concentration (denoted as $x_3$) were defined as follows:

$x_1 = 2 \times [T(°C) - 175] / (200 - 150)$ (eq. 2)

$x_2 = 2 \times [t(min) - 15] / (25 - 5)$ (eq. 3)

$x_3 = 2 \times [C(mM) - 2] / (3 - 1)$ (eq. 4)

The dependent variables were evaluated as a sum of the contribution of the independent variables (including first order, interaction and second-order terms), according to the generalized expression:

$y_j = b_{0j} + \sum_i b_{ij} x_j + \sum_i \sum_k b_{ikj} x_i x_k$ (eq.5)

where:

- $y_j$ (j:1-4) stand for the considered dependent variables (fructose conversion, HMF yield, levulinic acid yield and unidentified products yield);
- $x_i$ or $x_k$ (i or k: 1-3, k≥i) are the independent dimensionless variables;
- $b_{0j...}b_{ikj}$ are the regression coefficients, calculated from the experimental data by multiple regression using the least-squares method;

The considered dependent variables to define the chemical changes taking place in the reaction media were defined as follows: $y_1$: fructose conversion (mol%), $y_2$: HMF yield (mol%), $y_3$: levulinic acid yield (mol%) and $y_4$: unidentified products yield (mol%). Their statistical significance was defined on the basis of the Student's t-test, the statistical parameters measuring the correlation ($R^2$) and the statistical significance of the models according to the Fisher's F-test.

The effect of the severity factor (SF) on the fructose dehydration to HMF was also investigated and it was defined as follows:

$$CS = \log(R_0) \qquad \text{(eq.6)}$$

with $R_0 = t \times e^{\frac{T-T_{ref}}{14.75}}$

where T is the reaction temperature (°C), $T_{ref}$ is the reference temperature (100 °C), t is the reaction time (min) and 14.75 is the fitted value of the arbitrary constant. This latter and the value of the reference temperature were selected on the basis of the literature.[4,38]

## Results and discussion

### Catalysts screening for HMF synthesis from fructose

A wide range of metal salts, containing Cu, Ni, K, Na and Al cations and sulfate, nitrate and chloride anions, was tested in the homogeneous fructose dehydration to HMF. The reactions were carried out at 180 °C for 20 minutes, adopting the fructose concentration of 10 wt%, and the metal salt concentration of 2 mM, corresponding to 0.36 mol%, evaluated respect to the substrate. The loading of fructose is one of the highest up to now reported in the literature, while the adopted amount of catalyst is one of the lowest, being generally the first value under 6 wt% and the second one higher than 20 mM.[1] A blank test in the absence of catalyst (autohydrolysis reaction) was also performed and the results are compared in Figure 1.

Figure 1, near here

The conversion of fructose in the blank run was lower than those obtained in the catalytic ones, evidencing that all the employed metal salts certainly enhance the fructose conversion (Figure 1a). However, not all the tested catalysts showed a beneficial effect on reaction behavior. In fact, the aluminum salts led to the highest fructose conversions, but also to the lowest HMF yields and selectivities (Figure 1b), due to the formation of a great amount of both rehydration acids (Figure 1c) and unidentified products (Figure 1d). This is in agreement with Wang et al.[34] who studied

the conversion of fructose (5 wt%) to HMF in the biphasic system sec-butyl phenol/$H_2O$ = 2/1 vol./vol. at 160 °C with $AlCl_3$ (5 mM) as the catalyst. They found that the hydrolysis of the Al salt was significant, leading to the release of Al-containing cationic species (strong Lewis acid) and protons, which strongly catalyzed the fructose conversion to undesired by-products, such as humins and rehydration acids. On the other hand, regarding the salts with cations different from Al, HMF selectivity was related to the nature of the anion. In fact, working with the same cation, such as Na, K, Ni and Cu, HMF selectivity increased with the following order: sulfate<chloride<nitrate (Fig. 1b). This behavior has been already ascertained in the literature by Wu et al.[33] for potassium salts. Now, this effect has been verified for a wider range of metal salts, proving that sulfate anion really enhances the formation of by-products slightly more than the other anions, in particular to give heavier humins (Fig. 1d). Comparing the catalytic performances of salts with the same anion, it is possible to appreciate that copper salts led to the highest HMF yields and selectivity, highlighting the effective behavior of $Cu^{2+}$ in the synthesis of HMF, as already found by Fachri et al.[12] and Yu et al.[39] The reason of this enhancement toward HMF by $Cu^{2+}$ has been just discussed in the literature. It is reasonable to suppose that the high activity of $Cu^{2+}$ can be related to the great stability of the bidentate complex that $Cu^{2+}$ can form with the carbocation,[40] deriving from the elimination of the first water molecule from protonated fructose (Scheme S1).[12,41] In this way, $Cu^{2+}$ can polarize the C-O bond of the carbocation, facilitating the rate-determining internal hydride shift to the electron-deficient carbon. This limiting step is characterized by the activation energy of 26.3 kcal/mol[42] and leads to a tetrahydrofuran aldehyde, the subsequent loss of two water molecules affording HMF.[41]

In this supposed mechanism $Cu(NO_3)_2$ should act as Lewis acid. In order to prove this statement, the reaction was replicated under the same reaction conditions (180 °C, 20

min, pH of 4.6) starting from glucose and the results were compared with those ascertained with $HNO_3$. In the presence of $Cu(NO_3)_2$, the glucose conversion of 43.8 mol% and the HMF yield of 9.6 mol% were reached, both higher than those obtained in the presence $HNO_3$, which resulted 21.2 and 3.7 mol%, respectively. These runs indirectly proved that $Cu(NO_3)_2$ effectively acts as Lewis acid because, as it is well-known, the conversion of glucose is catalyzed by this type of acidity.[43] Moreover, in order to confirm the peculiar role of $Cu^{2+}$ on the reaction and the influence of $HNO_3$ formed during the salt hydrolysis, the fructose dehydration was studied under the same reaction conditions (180 °C, 20 min, pH of 4.6) employing $HNO_3$ as catalyst. In this last case, the fructose conversion of 59.6 mol% and the HMF selectivity of 52.0 mol% were reached, which were lower than those ascertained with $Cu(NO_3)_2$. On the other hand, when the reaction was performed in the presence of $HNO_3$ at 180 °C for 20 min but at pH = 2.4, i.e. introducing the same concentration of nitrate anions of the reference run with $Cu(NO_3)_2$, significantly lower HMF selectivity (42.3 mol%) was ascertained. In fact, the enhanced acidity favored higher HMF rehydration extent to formic and levulinic acids (sel. 14.9 mol %), together with increased formation of unidentified products (sel. 36.4 mol %). These results well evidence the key role of $Cu^{2+}$ on the activation of fructose conversion to HMF, in agreement with the proposed mechanism reported in Scheme S1. Moreover, another hypothesis reported by Jia et al.[44] was that $Cu^{2+}$ can inhibit the oxidative C-C bond cleavage of HMF and the radical reactions, which contribute to the humins formation. This was verified by the formation of insoluble humins. In fact, when $Cu(NO_3)_2$ was employed as catalyst, insoluble humins formation was observed after 5 days from the reaction, whereas, when a stronger acid catalyst, such as $Al(NO_3)_3$, was adopted, insoluble humins were immediately present, as confirmed by the photos and the FT-IR spectrum of the recovered solid reported in Figures S2 and S3, respectively. In this regard, at the moment, thermodynamics studies

using density function theory calculations are in progress. All the above peculiarities of $Cu^{2+}$ determine the high HMF selectivity ascertained employing copper salts, the highest HMF selectivity being obtained with $Cu(NO_3)_2$ (63.2 mol%). Therefore, under absolutely sustainable reaction conditions (MW heating, 10 wt% fructose concentration, 2 mM $Cu(NO_3)_2$, 180°C, 20 minutes), the highest HMF yield of 53.7 mol% was achieved, which is a remarkable value, higher than the majority reported in the literature for aqueous systems. The catalyst $Cu(NO_3)_2$ contributes to the whole sustainability of the process, being active at low concentrations, inexpensive, scarcely toxic, and, at the same time assisting also the catalysis of the subsequent HMF oxidation or reduction steps.[41] To the best of our knowledge, for the first time, $Cu(NO_3)_2$ is proposed as catalyst for fructose dehydration in water under microwave heating. Up to now, the employment of $Cu(NO_3)_2$ as catalyst for sugars dehydration was studied only by Sampath et al., who adopted this salt as co-catalyst together with $Al_2O_3$ for the dehydration of glucose to HMF in dimethylsulfoxide under conventional heating.[17]

Figure S4 reports the kinetic profile of fructose dehydration performed at 180 °C with 2 mM of $Cu(NO_3)_2$. Under the adopted reaction conditions, the highest HMF yield (53.7 mol%) was ascertained after 20 minutes: the further extension of the reaction time resulted detrimental for both HMF selectivity and yield, due to the significant formation of by-products, such as rehydration acids and humins. On the basis of the above really promising results, the optimization of HMF synthesis from fructose catalyzed by $Cu(NO_3)_2$ was carried out.

**Optimization of HMF synthesis from fructose solution through statistical modelling**

MW-assisted HMF synthesis from fructose, in the presence of $Cu(NO_3)_2$ as catalyst, is influenced by many independent variables, such as temperature, reaction time, catalyst concentration and fructose starting loading. In order to study this complex system,

optimize HMF synthesis and achieve a quantitative interpretation of the investigated phenomena, the Response Surface Methodology (RSM) analysis may be a useful tool. The most influential parameters were selected on the basis of previous studies and they were considered as independent variables in the statistical design: temperature ($x_1$), reaction time ($x_2$) and $Cu(NO_3)_2$ concentration ($x_3$). On the basis of the results obtained in the preliminary runs, the initial fructose concentration at 10 wt% and the variation ranges of the independent variables were fixed. Table 2 shows the dimensionless and dimensional independent variables adopted in the experimental design, together with the dependent variables considered to measure the chemical changes taking place during the reaction (fructose conversion ($y_1$), HMF yield ($y_2$), levulinic acid yield ($y_3$) and unidentified products yield ($y_4$)) and their experimental values.

Table 2, near here

According to Table 2, fructose conversion was low working under mild reaction conditions (runs 1 and 3), whereas high temperature and prolonged reaction time were necessary to reach the complete fructose conversion (runs 6, 8 and 10). HMF was detected in each run but the highest yields were achieved under conditions of intermediate severity (runs 5, 7, 14 and 15). In fact, adopting too harsh conditions, the decomposition of HMF became favored and higher yields of levulinic acid and unidentified products were ascertained (runs 6, 8, 10). Differently from levulinic acid, which was only formed under conditions of intermediate or high severity, the unidentified products were also present under mild reaction conditions, even though in low amounts (runs 1, 3 and 9), probably due to the prevailing substrate decomposition.[13] Concerning the RSM modelling of data, Table 3 lists the values calculated for the set of regression coefficients involved in the equations describing the behaviour of the dependent variables $y_1$, $y_2$, $y_3$ and $y_4$ (calculated according to eq. 5), together with their statistical significance, assessed on the basis of the Student's *t*-test. The same Table also

includes the statistical Fisher's F and $R^2$ parameters, which measure the significance and the correlation of the model, respectively.

Table 3, near here

Both values of Fisher's F and $R^2$ parameters indicated that our model is useful for predicting fructose conversion, HMF yield, levulinic acid yield and unidentified products yield. Moreover, Figure S5 shows the parity plot of fructose conversion and HMF yield, underlining the close relationship between the observed values and the predicted ones, confirming the high value for $R^2$.

In Table 3, the coefficients calculated for the fructose conversion ($y_1$) confirmed that this variable was strongly positively affected by temperature and reaction time, whereas the concentration of $Cu(NO_3)_2$ showed a very low influence. Therefore, an increment of temperature and/or reaction time led to an improvement of fructose conversion, which ranged between 10.3 and 100 mol% in the runs of the model. The response surface calculated for fructose conversion as a function of reaction time and temperature, operating at the intermediate $Cu(NO_3)_2$ concentration ($x_3$=0) is reported in Figure S6. The graph shows that temperature had a very strong influence on the fructose conversion, as confirmed by the calculated coefficients ($b_{1j}>b_{2j}$) and fructose conversions higher than 90 mol% were predicted at 190 °C for reaction time longer than 20 minutes or at higher temperature and shorter reaction time. Total fructose conversion was expected at 200 °C after 22 minutes.

The calculated coefficients for HMF yield ($y_2$) highlight that this variable was mainly positively affected by temperature, but, on the other hand, the temperature-time interaction term played a significant negative influence (Table 3). Figure 2a shows the response surface of HMF yield ($y_2$) calculated as function of $Cu(NO_3)_2$ concentration and reaction time at the maximum temperature ($x_1$=1), whereas Figure 2b shows the dependence of HMF yield ($y_2$) on $Cu(NO_3)_2$ concentration and temperature at

intermediate reaction time ($x_2$=0). Both these graphs underline that no significant effects were observed on HMF yield by salt concentration within the tested range.

Figure 2, near here

Figure 2c reports the response surface calculated for $y_2$ as a function of temperature and reaction time at the maximum $Cu(NO_3)_2$ concentration ($x_3$=1). The highest HMF yields (about 50 mol%) were predicted for times not longer than 14 minutes and temperatures between 180-195 °C, because at 200 °C the decomposition of HMF was strongly activated, even at short reaction time. The model predicts the highest HMF yield of 50.5 mol% at 188 °C for 9 minutes with the salt concentration of 3 mM. The fructose dehydration was carried out adopting these conditions, obtaining the fructose conversion of 83.9 mol% together with HMF selectivity of 64.4 mol%, corresponding to an experimental HMF yield of 54.0 mol%, demonstrating the good prediction of the models.

Regarding the yields of levulinic acid ($y_3$) and unidentified products ($y_4$), they mainly positively depended on both temperature and reaction time and the first parameter was also strongly positively influenced by the temperature-time interaction term (Table 3). Figures 3a and 3b report respectively the response surface of $y_3$ and $y_4$ calculated for the maximum $Cu(NO_3)_2$ concentration ($x_3$=1).

Figure 3, near here

According to runs 1, 2, 3 and 9 of Table 2, the levulinic acid yield resulted negligible for mild reaction conditions, being absent for temperatures lower than 175 °C. However, the increase of temperature and reaction time led to an evident improvement of levulinic acid yield, which showed an exponential trend, reaching the maximum value of 13.3 mol% at 200 °C after 25 minutes. The same trend was also found for the yield of unidentified products but, according to the results of the experimental design, the value of this variable was always appreciable in the whole investigated range and

reached its maximum value of 62.1 mol% at 200 °C after 25 minutes. It is important to underline that these harsh reaction conditions, addressing the synthesis towards the by-products, prevented HMF isolation, confirming that under these severe conditions HMF decomposition was enhanced.

Finally, the effect of the severity factor (SF) was also studied. This parameter has been successfully applied to the interpretation of hydrothermal biomass pre-treatment,[4] and during the recent years, it has been also employed as a significant parameter for the study of levulinic acid[45] and HMF[46] synthesis. Figure S7 reports the influence of SF on the fructose conversion and HMF yield. Fructose conversion increased along with the increasing of SF, reaching the complete conversion at the SF value of 3.8. On the other hand, HMF yield showed a peaked pattern, achieving the maximum value (54.0 mol%) at the SF of 3.55, which corresponds to the optimized reaction conditions found in the statistical modelling.

**HMF synthesis from inulin**

Inulin is a biopolymer consisting of a long chain of D-fructose units with D-glucose terminal units. It is present in a wide range of plant roots, such as dahlia and Jerusalem artichoke tubers and chicory roots, in an average amount of about 15-20 wt%, based on fresh weight.[47] As reported in the literature,[12-14] inulin is readily hydrolyzed into monosaccharides, which can be converted to HMF, making this biopolymer and the inulin-rich plants a promising feedstock for HMF synthesis. On the basis of the results obtained by the Response Surface Methodology, in this work HMF synthesis from inulin was performed under the reaction conditions optimized for fructose (initial substrate concentration 10 wt%, 188 °C, 9 minutes, 3 mM of $Cu(NO_3)_2$). Figure 4 reports the comparison between the fructose and inulin conversion to HMF.

Figure 4, near here

The achieved results confirmed that the hydrolysis of inulin was not the rate-limiting step and it was completely converted. Moreover, the conversion of the released fructose was high and comparable to that reached starting directly from this monosaccharide. HMF yield and selectivity achieved from inulin were only a little lower than those ascertained from fructose, due to slight higher amounts of by-products, in particular formic acid and unidentified products, whereas the levulinic acid yield remained almost unchanged. Up to now, few investigations have reported the conversion of inulin to HMF in water employing metal salts as catalyst. De et al.[30] and Fachri et al.[12] have studied this reaction in water under microwave irradiation adopting the initial inulin concentration of about 5 wt%, respectively in the presence of $AlCl_3$ (154 mM) and $CuCl_2$ (5 mM), reaching, under the best reaction conditions, HMF yields of 29 mol% (120 °C; 5 min) and 39 mol% (180 °C; 10 min). In our investigation, HMF yield up to 49.7 mol% was ascertained employing higher initial inulin concentration (10 wt%) and lower amount of catalyst ($Cu(NO_3)_2$ 3 mM). The obtained results are very promising because they open the way to the direct exploitation of inulin-rich raw biomasses, such as chicory root and Jerusalem artichoke (topinambur).

## Conclusion

The dehydration of fructose to HMF in water under sustainable reaction conditions was investigated. Different metal salts were tested for this reaction under MW heating, revealing that copper salts led to the best results, probably ascribable to the high stability of the $Cu^{2+}$ complex and to the ability of $Cu^{2+}$ of hampering the humins formation. $Cu(NO_3)_2$ was identified as the most efficient catalyst for HMF synthesis and the optimization of this reaction was also performed through a statistical modelling investigation. RSM analysis and the confirming experimental run indicated that the highest HMF yield, 54.0 mol%, was obtained at 188 °C after 9 minutes employing the catalyst concentration of 3 mM with the initial fructose concentration of 10 wt%. The

conversion of inulin to HMF was also studied under the optimized reaction conditions and almost comparable results were obtained. In conclusion, in this work, for the first time, $Cu(NO_3)_2$ was successfully employed for the sustainable conversion of fructose and inulin to HMF in water under MW heating. The significant yield reached adopting high substrate concentration and low catalyst loading makes this homogeneous catalyst really promising for the future direct exploitation of fructan-rich raw biomasses.

## Acknowledgments

The authors thank the PRIN 2015-Project HERCULES "Heterogeneous Robust Catalyst to Upgrade Low value biomass Streams" (code 20153T4REF).

## Supporting Information

$^{1}$H NMR and $^{13}$C NMR spectra of isolated HMF, detailed calculation of isolated HMF yield, HMF production on gram-scale, mechanism of fructose dehydration to HMF, photos of reaction mixtures, FT-IR spectrum of humins, kinetic profile, parity plots, response surface curve and severity factors graphs.

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**Caption for figures**

**Figure 1** a) Fructose conversion (mol%); b) HMF yield (mol%) and selectivity (mol%); c) Formic and levulinic acid yields (mol%); d) Unidentified products selectivity (mol %): all parameters as function of the metal catalysts. Reaction conditions: initial fructose concentration 10 wt%; salts concentration 2 mM; 180 °C; 20 minutes.

**Figure 2** Dependence of HMF yield ($y_2$) on: a) $Cu(NO_3)_2$ concentration and reaction time calculated for the maximum temperature ($x_1$=1); b) $Cu(NO_3)_2$ concentration and temperature calculated for the intermediate reaction time ($x_2$=0) ; c) reaction time and temperature calculated for the maximum $Cu(NO_3)_2$ concentration ($x_3$=1).

**Figure 3** Dependence of levulinic acid yield (a) and unidentified products yield (b) on reaction time and temperature calculated for the maximum $Cu(NO_3)_2$ concentration ($x_3$=1).

**Figure 4** Comparison between fructose and inulin conversion to HMF under the optimized reaction conditions (initial substrate concentration 10 wt%; $Cu(NO_3)_2$ concentration 3 mM; 188 °C; 9 min;).

**Table 1:** Summary of the most important literature results obtained in water for the fructose, glucose and inulin dehydration to HMF.

| Substrate conc. wt% | Catalyst (mM) | T (°C) | t (min) | Conv. (mol%) | HMF Yield (mol%) | Ref. |
|---|---|---|---|---|---|---|
| Fructose 10 wt% | $CrCl_3$ 18 mM | 140 | 60 | 87 | 21 | [26] |
| Glucose 10 wt% | $CrCl_3$ 18 mM | 140 | 90 | 78 | 16 | [26] |
| Fructose 1 wt% | $K_2NO_3$ 40 mM | 180 | 90 | 90 | 45 | [33] |
| Glucose 1 wt% | KCl 40 mM | 180 | 240 | 58 | 22 | [33] |
| Fructose[a] 5 wt% | $AlCl_3$ 139 mM | 120 | 5 | not determined | 55 | [30] |
| Glucose[a] 5 wt% | $AlCl_3$ 139 mM | 120 | 20 | not determined | 40 | [30] |
| Inulin[a] 5 wt% | $AlCl_3$ 139 mM | 120 | 5 | not determined | 29 | [30] |
| Fructose[a] 4 wt% | $FeCl_3$ 100 mM | 140 | 7 | 82 | 38 | [35] |
| Glucose[a] 4 wt% | $FeCl_3$ 100 mM | 140 | 40 | 20 | 5 | [35] |
| Inulin[a] 5 wt% | $CuCl_2$ 5 mM | 180 | 10 | not determined | 39 | [12] |

[a] reaction carried out under microwave heating

**Table 2:** Operational conditions defining the experiments assayed for HMF production and experimental values of the dependent variables.

| | **Dimensionless normalized variables** | | | **Dimensional variables** | | | **Dependent variables** | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Runs** | $x_1$ | $x_2$ | $x_3$ | **T (°C)** | **t (min)** | **C (mM)** | $y_1$ **(mol%)** | $y_2$ **(mol%)** | $y_3$ **(mol%)** | $y_4$ **(mol%)** |
| **1** | -1 | -1 | -1 | 150 | 5 | 1 | 10.3 | 3.9 | 0.0 | 6.1 |
| **2** | -1 | 1 | -1 | 150 | 25 | 1 | 33.7 | 7.8 | 0.0 | 25.9 |
| **3** | -1 | -1 | 1 | 150 | 5 | 3 | 14.6 | 5.9 | 0.0 | 8.7 |
| **4** | -1 | 1 | 1 | 150 | 25 | 3 | 40.5 | 11.1 | 0.2 | 26.9 |
| **5** | 1 | -1 | -1 | 200 | 5 | 1 | 77.0 | 43.3 | 1.0 | 30.4 |
| **6** | 1 | 1 | -1 | 200 | 25 | 1 | 98.7 | 24.1 | 11.6 | 57.6 |
| **7** | 1 | -1 | 1 | 200 | 5 | 3 | 94.7 | 50.5 | 3.8 | 32.9 |
| **8** | 1 | 1 | 1 | 200 | 25 | 3 | 100 | 21.7 | 12.8 | 62.1 |
| **9** | -1 | 0 | 0 | 150 | 15 | 2 | 21.0 | 9.8 | 0.0 | 11.2 |
| **10** | 1 | 0 | 0 | 200 | 15 | 2 | 98.6 | 37.7 | 10.0 | 46.0 |
| **11** | 0 | -1 | 0 | 175 | 5 | 2 | 42.8 | 26.9 | 0.2 | 12.4 |
| **12** | 0 | 1 | 0 | 175 | 25 | 2 | 85.5 | 41.5 | 3.5 | 31.7 |
| **13** | 0 | 0 | -1 | 175 | 15 | 1 | 55.4 | 37.3 | 0.5 | 14.0 |
| **14** | 0 | 0 | 1 | 175 | 15 | 3 | 80.4 | 47.9 | 2.0 | 24.8 |
| **15** | 0 | 0 | 0 | 175 | 15 | 2 | 67.9 | 44.5 | 1.2 | 17.1 |
| **16** | 0 | 0 | 0 | 175 | 15 | 2 | 68.1 | 43.4 | 1.3 | 19.1 |
| **17** | 0 | 0 | 0 | 175 | 15 | 2 | 69.4 | 42.5 | 1.2 | 21.0 |

**Table 3:** Regression coefficients ($b_{0j}...b_{23j}$) and statistical parameters measuring the correlation and significance of models.

| Parameter | Variables | | | |
|---|---|---|---|---|
| | $y_1$ | $y_2$ | $y_3$ | $y_4$ |
| $b_{0j}$ | 67.480* | 41.701* | 1.676* | 19.201* |
| $b_{1j}$ | 34.869* | 13.872* | 3.889* | 15.033* |
| $b_{2j}$ | 11.652* | -2.439 | 2.318* | 11.376* |
| $b_{3j}$ | 5.488*** | 2.060 | 0.568*** | 2.15** |
| $b_{11j}$ | -6.812 | -16.767* | 2.954* | 9.304* |
| $b_{22j}$ | -3.437 | -6.272 | -0.131 | 2.729 |
| $b_{33j}$ | 1.303 | 2.083 | -0.751 | 0.109 |
| $b_{12j}$ | -2.754 | -7.125** | 2.434* | 2.304*** |
| $b_{13j}$ | 1.044 | -0.055 | 0.466 | 0.414 |
| $b_{23j}$ | -1.719 | -1.028 | -0.174 | 0.044 |
| **Multiple correlation coefficient** | 0.986 | 0.965 | 0.990 | 0.993 |
| $R^2$ | 0.972 | 0.931 | 0.981 | 0.986 |
| **Adjusted $R^2$** | 0.936 | 0.843 | 0.956 | 0.969 |
| $F_{st}$ | 27.00 | 10.53 | 39.80 | 56.07 |

*Significance at 99%

**Significance at 95%

***Significance at 90%

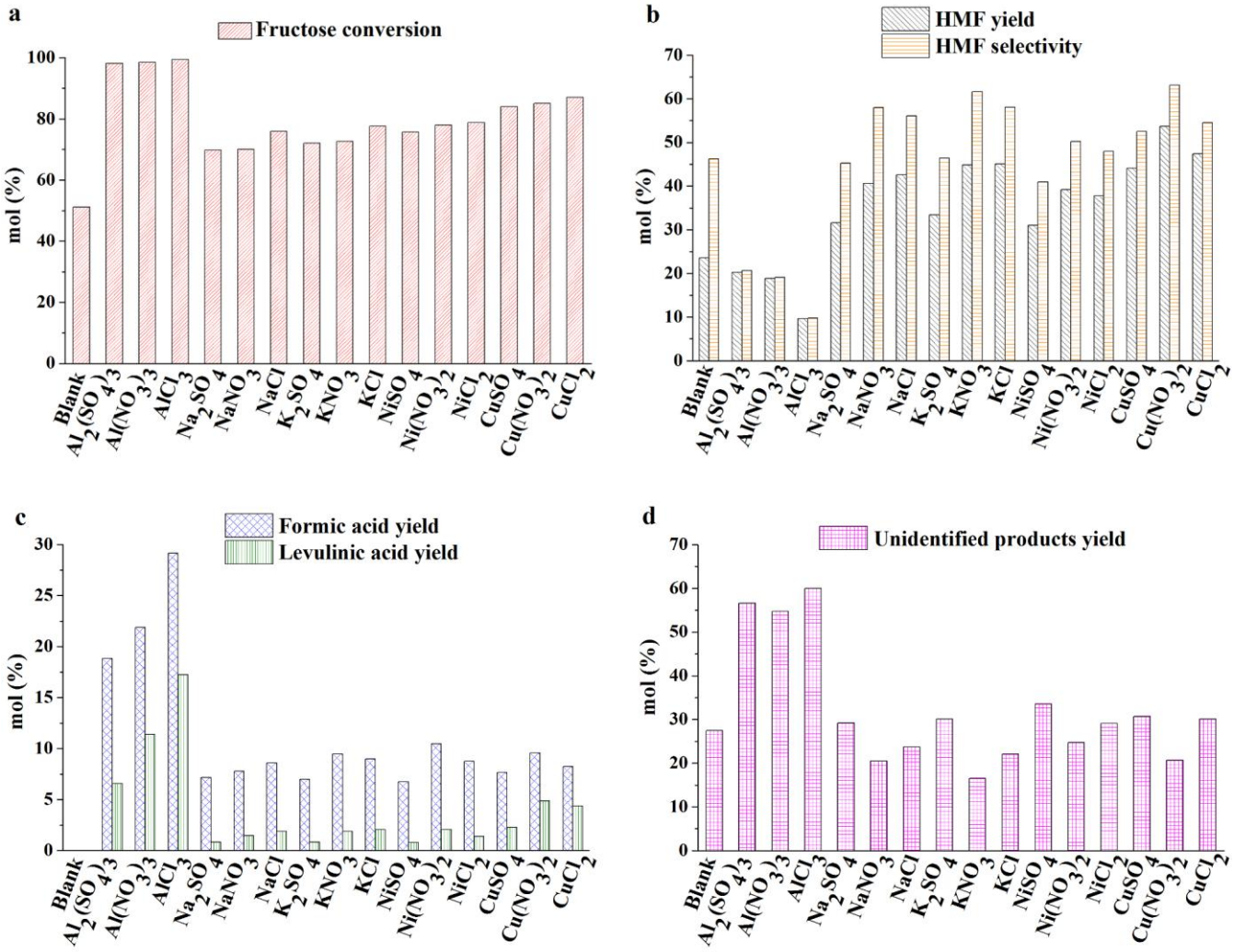
a
Fructose conversion
mol (%)
b
HMF yield
HMF selectivity
mol (%)
c
Formic acid yield
Levulinic acid yield
mol (%)
d
Unidentified products yield
mol (%)
Blank
Al2(SO4)3
Al(NO3)3
AlCl3
Na2SO4
NaNO3
NaCl
K2SO4
KNO3
KCl
NiSO4
Ni(NO3)2
NiCl2
CuSO4
Cu(NO3)2
CuCl2

**Figure 1**

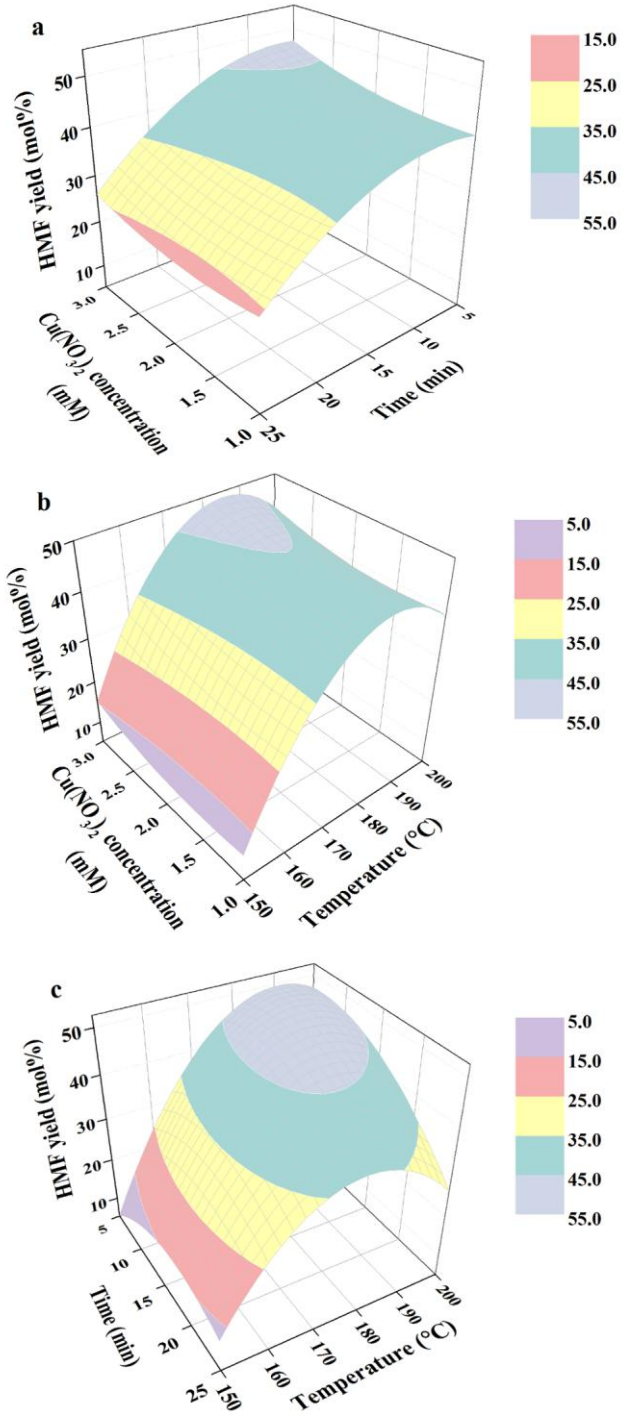
a
HMF yield (mol%)
50
40
30
20
10
3.0
2.5
2.0
1.5
1.0
Cu(NO3)2 concentration (mM)
25
20
15
10
5
Time (min)
15.0
25.0
35.0
45.0
55.0
b
HMF yield (mol%)
50
40
30
20
10
3.0
2.5
2.0
1.5
1.0
Cu(NO3)2 concentration (mM)
150
160
170
180
190
200
Temperature (°C)
5.0
15.0
25.0
35.0
45.0
55.0
c
HMF yield (mol%)
50
40
30
20
10
5
10
15
20
25
Time (min)
150
160
170
180
190
200
Temperature (°C)
5.0
15.0
25.0
35.0
45.0
55.0

**Figure 2**

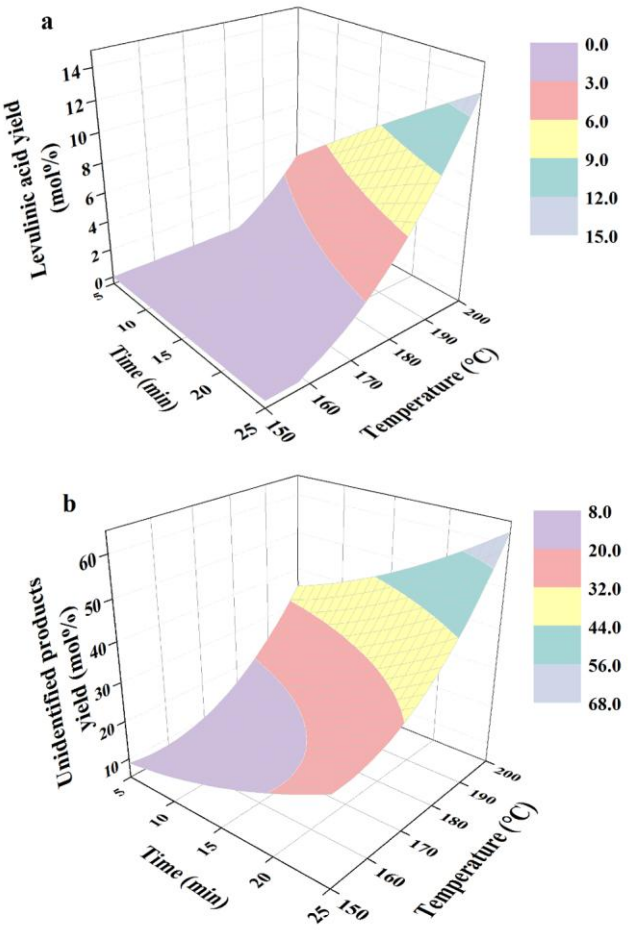
a
Levulinic acid yield (mol%)
0
2
4
6
8
10
12
14
Time (min)
5
10
15
20
25
Temperature (°C)
150
160
170
180
190
200
0.0
3.0
6.0
9.0
12.0
15.0
b
Unidentified products yield (mol%)
10
20
30
40
50
60
Time (min)
5
10
15
20
25
Temperature (°C)
150
160
170
180
190
200
8.0
20.0
32.0
44.0
56.0
68.0

**Figure 3**

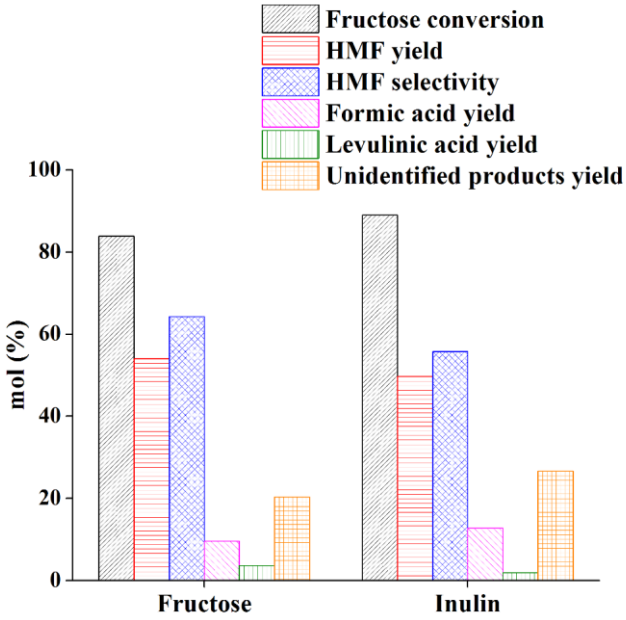
Fructose conversion
HMF yield
HMF selectivity
Formic acid yield
Levulinic acid yield
Unidentified products yield
mol (%)
100
80
60
40
20
0
Fructose
Inulin

**Figure 4**

# Supporting Information

## Turning point towards the sustainable production of HMF in water: metal salts for its synthesis from fructose and inulin

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Total number of pages: 9 (S1-S9)

Total number of figures: 7 (Figure S1-S7)

Total number of schemes: 1 (Scheme S1)

Total number of tables: 1 (Table S1)

## Table of Contents

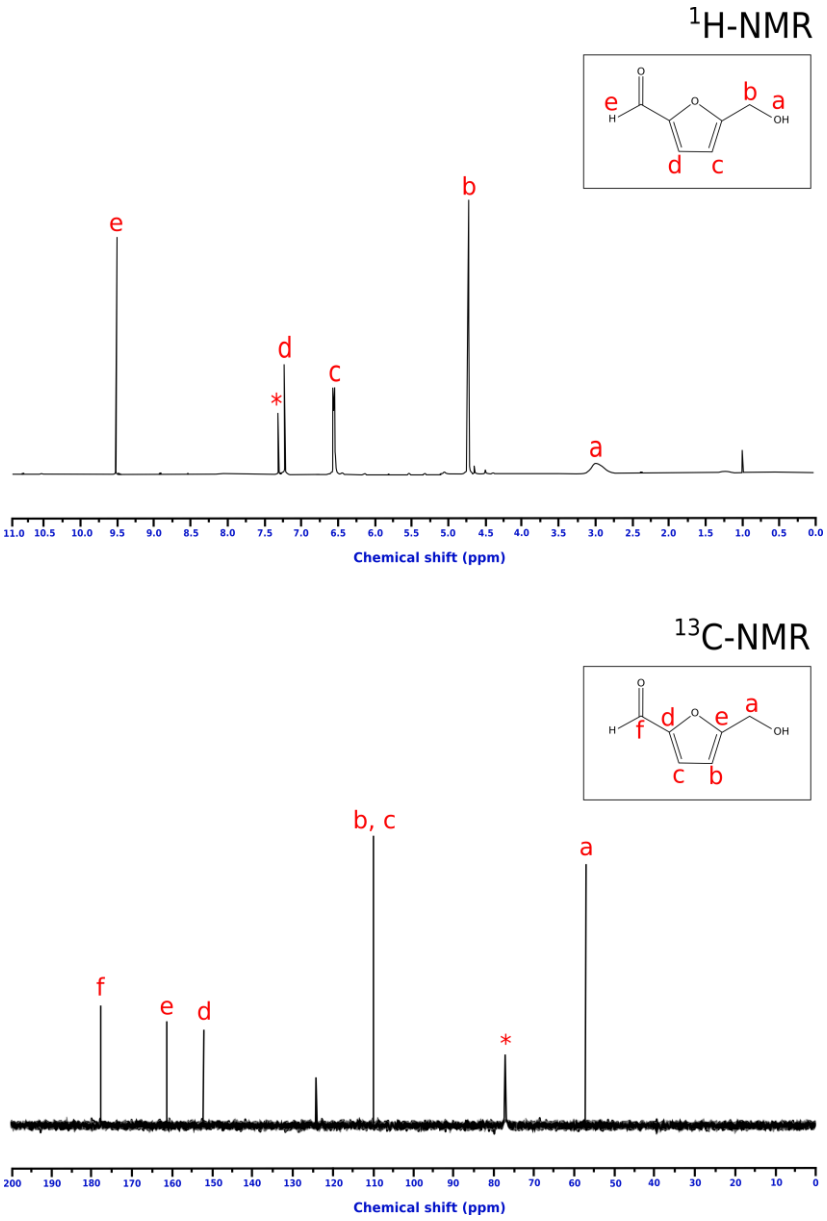



**Figure S1** $^{1}$H NMR and $^{13}$C NMR spectra of isolated HMF (* is the peak of chloroform).

## Calculation of isolated HMF yield

- HPLC-determined HMF yield was calculated by the ratio of the HMF moles from HPLC analysis and initial fructose moles and it was 54.0 mol%.

  The recovery HMF yield was calculated by the ratio of the HMF weight extracted by dichloromethane respect to the initial HMF content (by weight) in the hydrolyzate, taking into account that, on the basis of NMR analysis, the HMF purity grade was 94%. The equation is

reported below:

Recovery HMF yield = (weight $_{\text{isolated HMF}}$/weight $_{\text{HMF in hydrolyzate}}$) × 100 =

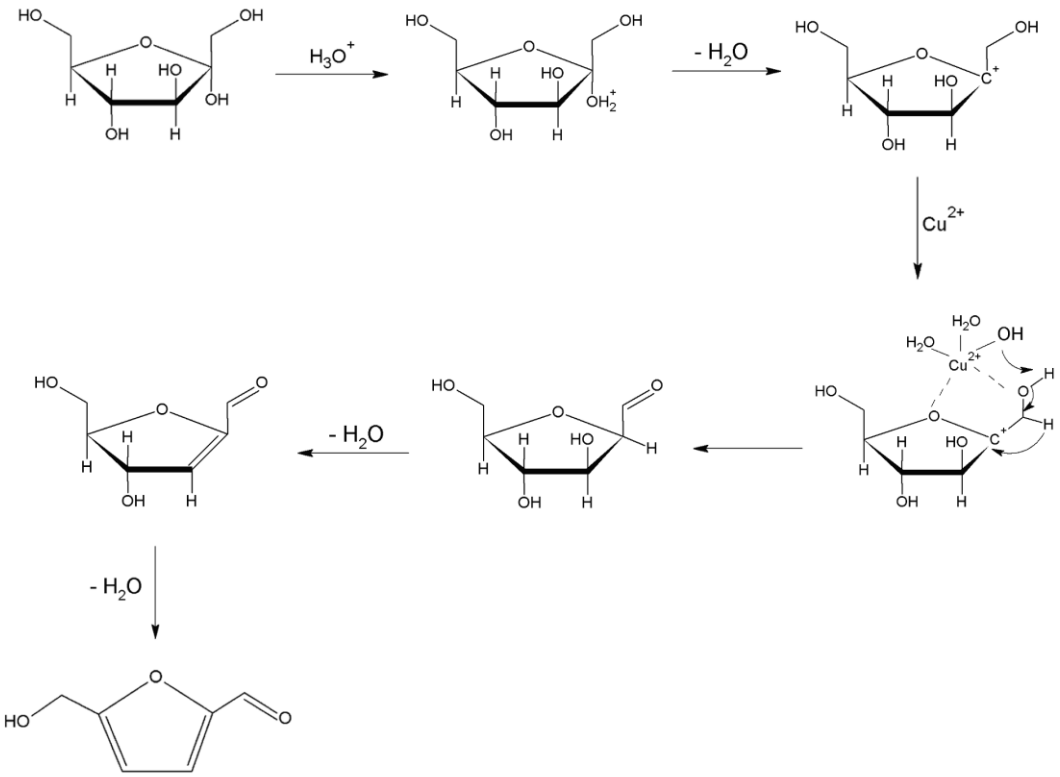
= (0.94 × weight $_{\text{recovered solid}}$/weight $_{\text{HMF in hydrolyzate}}$)

The recovery yield was 76.9%.

- The isolated HMF yield was calculated as the product between the HPLC-determined HMF yield and the recovery yield, resulting equal to 41.5 mol%.

**HMF production on gram-scale**

5.5 g of fructose and 0.028 g of $Cu(NO_3)_2$ were weighted and dissolved in 50 ml of water. The reaction was conducted in the microwave reactor at 188 °C for 9 min, these corresponding to the optimal reaction conditions on the basis of the statistical modelling. At the end of the reaction, the obtained hydrolyzate was filtered through syringe filter Whatman 0.45 μm PTFE, before the HPLC analysis, the latter confirming the HMF yield of 54 mol%. The hydrolyzate was subsequently extracted in a continuous liquid-liquid extractor apparatus for 4 h employing 150 ml of dichloromethane as extraction solvent. Then, once the organic fraction was separated, dichloromethane was removed by distillation under reduced pressure. The isolated yellow solid was recovered and weighted, resulting in 1.7 g. By the NMR analysis, the purity grade of isolated HMF was 94%, thus at the end of the process 1.6 g of pure HMF was achieved.




**Scheme S1** Proposed mechanism for fructose dehydration to HMF, in the presence of inorganic salts.

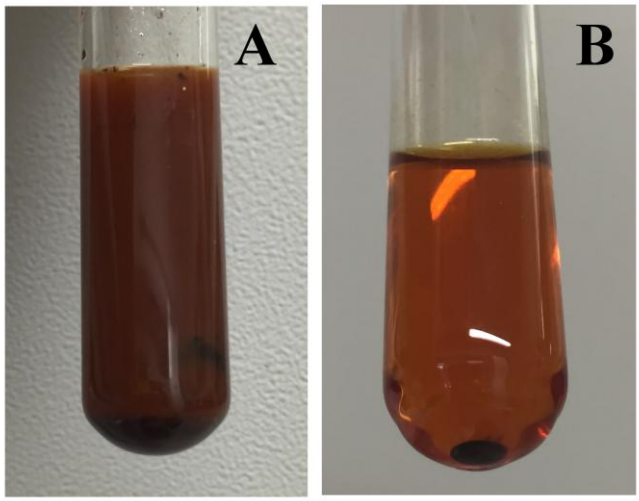



**Figure S2** Reaction mixtures obtained from the MW-assisted dehydration of fructose carried out at 180 °C for 20 minutes with the initial fructose concentration of 10 wt%, in the presence of different catalysts: A) $Al(NO_3)_3$; B) $Cu(NO_3)_2$. The photo A) was taken immediately after the reaction; the photo B) was taken 5 days after the reaction.

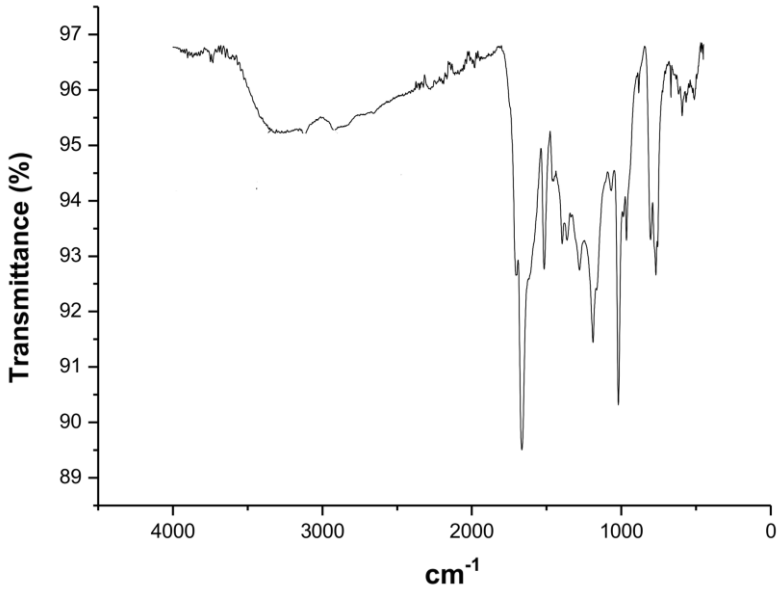



**Figure S3** FT-IR spectrum of the solid recovered from the reaction with $Al(NO_3)_3$.

**Table S1** Assignment of IR bands reported in Figure S3.

| **Wavenumber ($cm^{-1}$)** | **Assignment** |
|---|---|
| 3300 | stretching O-H of hydroxyl or carboxyl group |
| 2920 | stretching C-H of aliphatic group |
| 1705 | stretching C=O of aldehydes and ketones |
| 1664 | stretching C=O of quinones |
| 1515 | stretching C=C of furan ring |
| 1395 | stretching C-O-C of furanyl ether |
| 1279<br>1189<br>1022 | stretching C-O of aliphatic alcohols and ethers |
| 875-750 | aromatic/furanic C-H bending out of plane |

The correspondence of the IR absorption bands of the recovered solid with those typical of humins[1-4] unequivocally confirms their significant presence in the solid residue.

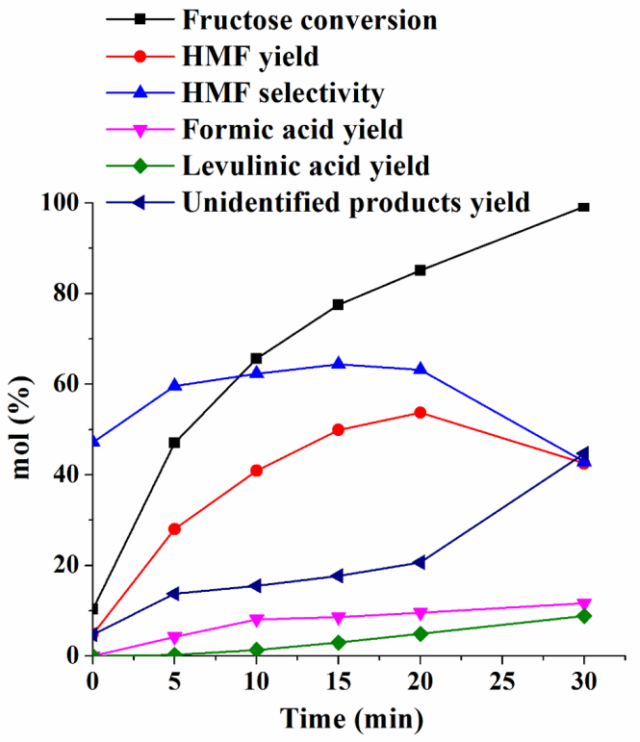



**Figure S4** Kinetic profile of fructose dehydration at 180 °C with 2mM of $Cu(NO_3)_2$.

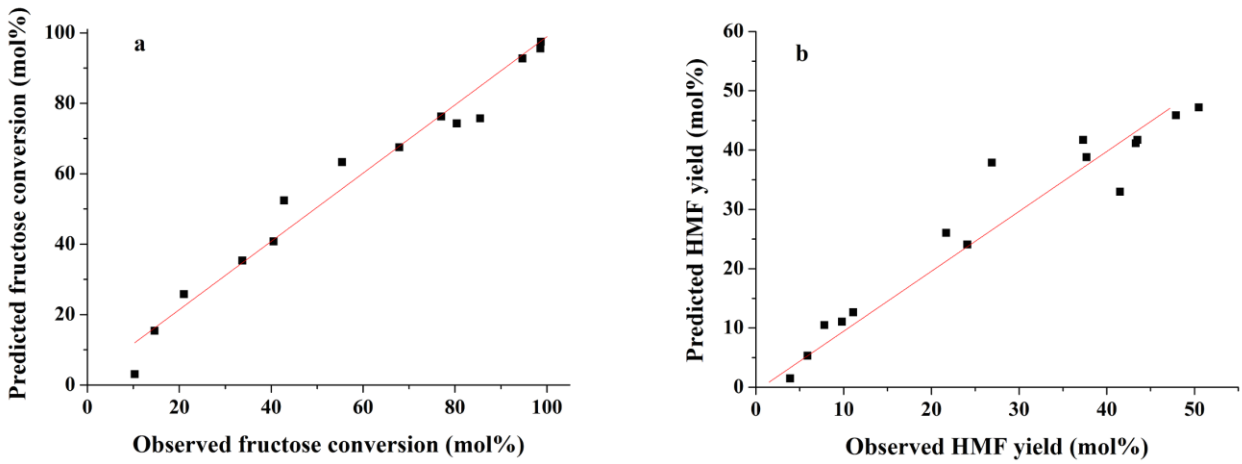



**Figure S5** Parity plot of: a) fructose conversion and b) HMF yield.

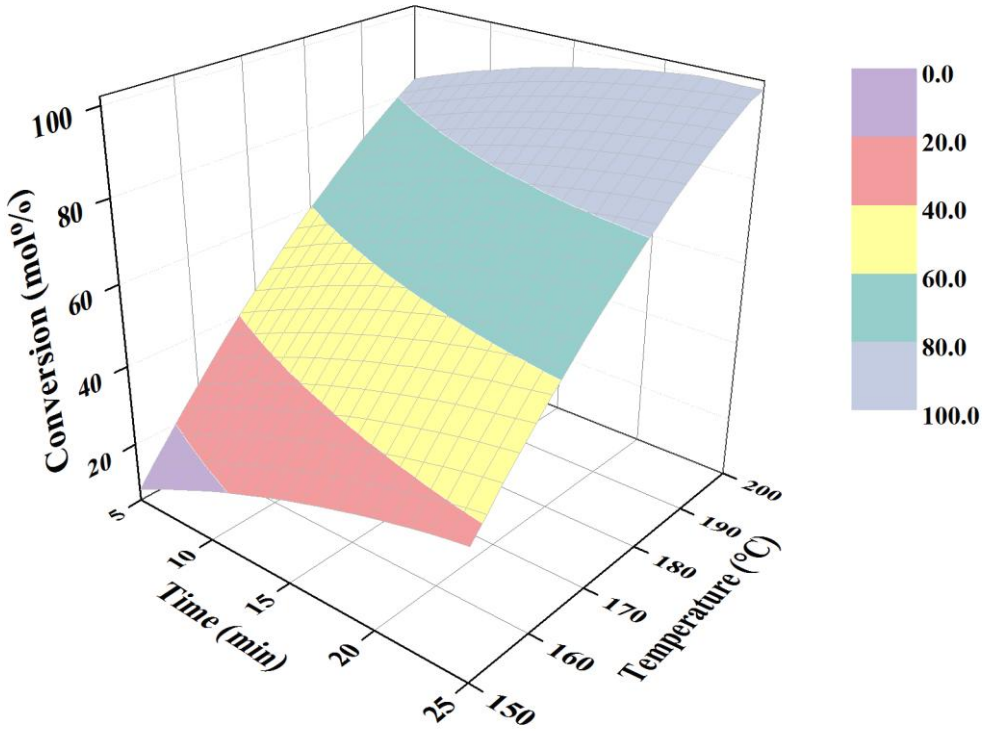



**Figure S6** Dependence of fructose conversion ($y_1$) versus reaction time and temperature, calculated for the intermediate $Cu(NO_3)_2$ concentration ($x_3$=0).

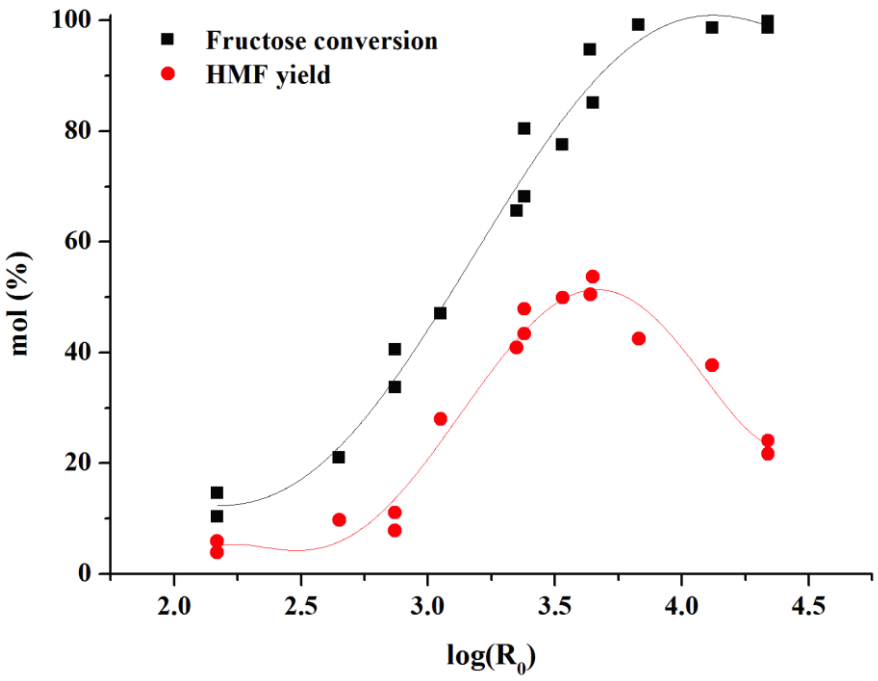



**Figure S7** Effect of severity factor on fructose conversion (■) and HMF yield (•) in the fructose dehydration catalysed by $Cu(NO_3)_2$.

## References

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# Graphical Abstract